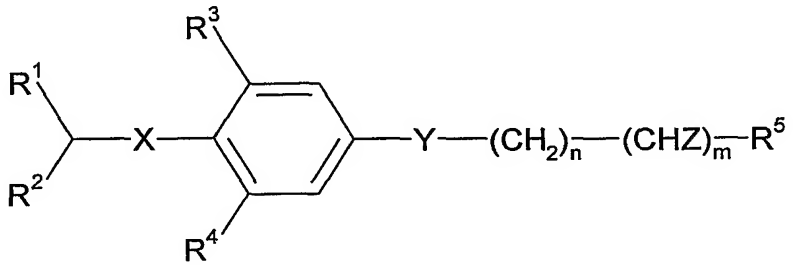
Claims

1. A compound of formula (I) or a pharmaceutically acceptable ester, amide, solvate or salt thereof, including a salt of such an ester or amide, and a solvate of such an ester, amide or salt, for use in the treatment or prophylaxis of a condition mediated by an androgen receptor,



(I)

wherein:

R^1 is selected from C_{5-10} aryl, C(O)-C_{5-10} aryl, C(O)-C_{3-8} heterocyclyl, C_{5-10} aryl-C_{1-2} alkyl, C_{3-10} heterocyclyl, C_{3-10} heterocyclyl-C_{1-2} alkyl, C_{3-15} alkyl, C_{4-15} alkenyl, C_{3-15} alkynyl, C_{3-10} cycloalkyl and C_{3-10}cycloalkylC_{1-2}alkyl, said alkyl, alkenyl and alkynyl groups or portions of groups optionally being substituted with, where applicable, 1 to 3 groups R^a which may be the same or different; said heterocyclyl and cycloalkyl groups or portions of groups optionally being substituted with, where applicable, 1 to 3 groups $R^{a'}$ which may be the same or different; said aryl groups or portions of groups optionally being substituted with, where applicable, 1 to 4 groups $R^{a''}$ which may be the same or different;

R^2 is selected from hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl and C_{1-4} alkoxy;

or R^1 and R^2 together with the carbon atom to which they are both attached form a C_{4-8} cycloalkyl, C_{4-8} cycloalkenyl, a saturated or partially saturated C_{3-10} heterocyclyl,

optionally substituted with, where applicable, 1 to 3 groups $R^{a'}$ which may be the same or different;

X is selected from CH_2, oxygen, sulfur, sulfoxide, sulfone, selenium, tellurium, disulfide, and a group of formula -N(R^c)-;

R^3 and R^4 are independently selected from hydrogen, halogen, C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{3-7} heterocyclyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio, trifluoromethylthio, and $COOR^c$;

Y is selected from bond, carbonyl, oxygen, sulphur, -CH(R^b)-, -NHCO-, -CONH-, -$NHSO_2$-, -SO_2NH-, -N(R^c)- and -CR^6=CR^7-;

n is selected from 0, 1, 2 and 3;

Z is selected from halogen, amino, hydroxy, mercapto, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy and $(CH_2)_pOH$, where p is an integer from 1 to 4;

m is selected from 0 and 1;

R^5 is selected from -CO_2R^c, -$PO(OR^c)_2$, -$PO(OR^c)NH_2$, -SO_2OR^c, -$COCO_2R^c$, $CONR^cOR^c$, -SO_2NHR^c, -$NHSO_2R^{c'}$, -$CONHSO_2R^{c'}$, and - SO_2NHCOR^c;

R^6 and R^7 are independently selected from hydrogen, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{5-10}aryl, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, and $(CH_2)_pOH$, where p is an integer from 1 to 4;

R^a is selected from halogen, C_{1-4} alkoxy, C_{5-10} aryl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio, trifluoromethylthio, mercapto, cyano, and nitro;

$R^{a'}$ is selected from R^a, fluoromethyl, difluoromethyl, trifluoromethyl, C_{1-4} alkyl, C_{3-10} heterocyclyl-C_{2-4} alkenyl, C_{5-10}aryl-C_{2-4}alkenyl, C_{3-10} heterocyclyl-C_{1-4} alkyl and C_{5-10}aryl-C_{1-4} alkyl;

$R^{a''}$ is selected from:

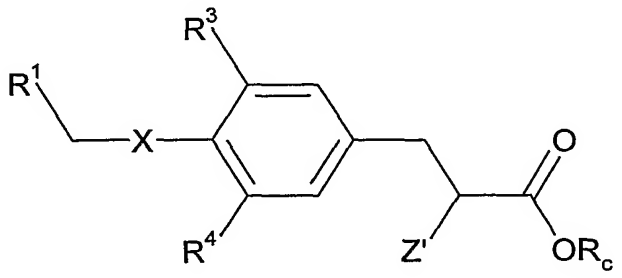
- $R^{a'}$;
- C_{2-4} alkenyl, optionally substituted with 1, 2 or 3 groups selected from C_{5-10} aryl, $C(O)R^c$, C_{3-10} heterocyclyl, and C_{3-10} heterocyclyl substituted with C_{1-4} alkyl;
- C_{2-8} alkenyloxy;
- C_{3-8} cycloalkyl-C_{1-3} alkoxy, C_{5-10} aryl-C_{1-3} alkoxy, and C_{5-10} aryloxy, said C_{3-8} cycloalkyl-C_{1-3} alkoxy, C_{5-10} aryl-C_{1-3} alkoxy or C_{5-10} aryloxy optionally being substituted with 1, 2 or 3 groups selected from C_{1-4} alkyl, halogen, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, mercapto, hydroxy, cyano, nitro, a group of formula $-N(R^c)_2$ in which the two R^c groups may be the same or different but not both simultaneously hydrogen;

R^b is selected from hydrogen, halogen, hydroxyl, mercapto, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy and $(CH_2)_pOH$, where p is an integer from 1 to 4; and

R^c is selected from hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl and C_{2-4} alkynyl; and

$R^{c'}$ is selected from R^c, C_{5-10} aryl and C_{5-10} aryl substituted with 1, 2 or 3 groups selected from amino, hydroxy, halogen or C_{1-4} alkyl.

2. A compound as claimed in claim 1 which is of formula (Ia) or a pharmaceutically acceptable ester, amide, solvate or salt thereof, including a salt of such an ester or amide, and a solvate of such an ester, amide or salt, for use in the treatment or prophylaxis of a condition mediated by an androgen receptor,



(Ia)

wherein:

R^1 is selected from C_{6-10} aryl, C_{5-10} heterocyclyl-C_{1-2}-alkyl, C_{4-10} alkyl and C_{5-7} cycloalkyl, said alkyl optionally being substituted with, where applicable, 1 to 3 groups R^a which may be the same or different; said cycloalkyl optionally being substituted with, where applicable, 1 to 3 groups $R^{a'}$ which may be the same or different; and said aryl optionally being substituted with, where applicable, 1 to 3 groups $R^{a''}$ which may be the same or different;

X is selected from oxygen and sulfur;

R^3 and R^4 are independently selected from hydrogen, halogen, C_{1-2} alkyl, C_{1-2} alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy and trifluoromethoxy;

Z' is selected from hydrogen, halogen, hydroxyl and mercapto;

R^a is selected from halogen, C_{5-10}aryl, fluoromethoxy, difluoromethoxy, trifluoromethoxy and nitro;

$R^{a'}$ is selected from R^a, fluoromethyl, difluoromethyl, trifluoromethyl, C_{1-4} alkyl C_{5-10} heterocyclyl-C_{2-4} alkenyl, C_{5-10}aryl-C_{2-4}alkenyl, C_{5-10} heterocyclyl-C_{1-4} alkyl and C_{5-10}aryl-C_{1-4} alkyl;

$R^{a''}$ is selected from:

- $R^{a'}$;
- C_{2-4} alkenyl, substituted with C_{3-10} heterocyclyl;
- C_{5-10} aryloxy, optionally being substituted with 1, 2 or 3 groups selected from C_{1-4} alkyl, halogen, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, mercapto, hydroxy, cyano, or nitro;

and

R^c is selected from hydrogen and C_{1-4} alkyl.

3. A compound as claimed in claim 1 or claim 2 whereby the condition mediated by an androgen receptor is selected from the group consisting of: prostate cancer, psychological abnormalities (including mood (depression, aggression, anxiety) and cognitive function), male pattern baldness (alopecia), benign prostatic hyperplasia (BPH), amenorrhea, hypogonadism, anemia, defects in spermatogenesis, cachexia, osteoporosis, osteopenia, and muscle wasting.

4. A method for the treatment or prophylaxis of a condition in a mammal mediated by an androgen receptor, which comprises administering to the mammal a therapeutically effective amount of a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable ester, amide, solvate or salt thereof, including a salt of such an ester or amide, and a solvate of such an ester, amide or salt.

5. Use of a compound of formula (I) as defined in claim 1 or a compound of formula (Ia) as defined in claim 2, or a pharmaceutically acceptable ester, amide, solvate or salt

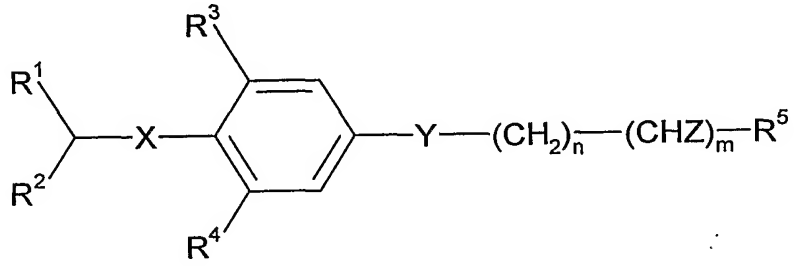
thereof, including a salt of such an ester or amide, and a solvate of such an ester, amide or salt, for the manufacture of a medicament for the treatment or prophylaxis of a condition mediated by an androgen receptor.

6. A pharmaceutical formulation comprising a compound of formula (I) as defined in claim 1 or a compound of formula (Ia) as defined in claim 2, or a pharmaceutically acceptable ester, amide, solvate or salt thereof, including a salt of such an ester or amide, and a solvate of such an ester, amide or salt, and a pharmaceutically acceptable excipient.

7. Use of a compound as defined in claim 1 or claim 2 in labelled form as a diagnostic agent for the diagnosis of conditions associated with malfunction of the androgen receptor.

8. A method of discovering a ligand of the androgen receptor which comprising use of a compound as defined in claim 1 or claim 2 or a compound as defined in claim 1 or claim 2 in labelled form, as a reference compound.

9. A compound of formula (Ib) or a pharmaceutically acceptable ester, amide, solvate or salt thereof, including a salt of such an ester or amide, and a solvate of such an ester, amide or salt,



(Ib)

wherein:

R^1 is selected from C_{5-10} aryl, C(O)-C_{5-10} aryl, C(O)-C_{3-8} heterocyclyl, C_{5-10} aryl-C_{1-2} alkyl, C_{3-10} heterocyclyl, C_{3-10} heterocyclyl-C_{1-2} alkyl, C_{3-15} alkyl, C_{4-15} alkenyl, C_{3-15} alkynyl, C_{3-10} cycloalkyl and C_{3-10}cycloalkylC_{1-2}alkyl, said alkyl, alkenyl and alkynyl optionally being substituted with, where applicable, 1 to 3 groups R^a which may be the same or different; said aryl-alkyl, heterocyclyl and cycloalkyl optionally being substituted with, where applicable, 1 to 3 groups $R^{a'}$ which may be the same or different; said aryl optionally being substituted with, where applicable, 1 to 4 groups $R^{a''}$ which may be the same or different;

R^2 is selected from hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl and C_{1-4} alkoxy;

or R^1 and R^2 together with the carbon atom to which they are both attached form a C_{4-8} cycloalkyl, C_{4-8} cycloalkenyl, a saturated or partially saturated C_{3-10} heterocyclyl, optionally substituted with, where applicable, 1 to 3 groups $R^{a'}$ which may be the same or different;

X is selected from CH_2, oxygen, sulfur, sulfoxide, sulfone, selenium, tellurium, disulfide, and a group of formula -N(R^c)-;

R^3 and R^4 are independently selected from hydrogen, halogen, C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{3-7} heterocyclyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio, trifluoromethylthio, and $COOR^c$;

Y is selected from bond, carbonyl, oxygen, sulphur, -CH(R^b)-, -NHCO-, -$NHSO_2$-, -SO_2NH-, -N(R^c)- and -CR^6=CR^7-;

n is selected from 0, 1, 2 and 3;

Z is selected from halogen, amino, hydroxy, mercapto, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy and $(CH_2)_pOH$, where p is an integer from 1 to 4;

R^5 is selected from $-CO_2R^c$, $-PO(OR^c)_2$, $-PO(OR^c)NH_2$, $-SO_2OR^c$, $-COCO_2R^c$, $CONR^cOR^c$, $-SO_2NHR^c$, $-NHSO_2R^{c'}$, $-CONHSO_2R^c$, and $-SO_2NHCOR^c$;

R^6 and R^7 are independently selected from hydrogen, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{5-10}aryl, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, and $(CH_2)_pOH$, where p is an integer from 1 to 4;

R^a is selected from halogen, C_{1-4} alkoxy, C_{5-10} aryl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio, trifluoromethylthio, mercapto, cyano, and nitro;

$R^{a'}$ is selected from R^a, fluoromethyl, difluoromethyl, trifluoromethyl, C_{1-4} alkyl, C_{3-10} heterocyclyl-C_{2-4} alkenyl, C_{5-10}aryl-C_{2-4}alkenyl, C_{3-10} heterocyclyl-C_{1-4} alkyl and C_{5-10}aryl-C_{1-4} alkyl;

$R^{a''}$ is selected from:

- $R^{a'}$;
- C_{2-4} alkenyl, optionally substituted with 1, 2 or 3 groups selected from C_{5-10} aryl, $C(O)R^c$, C_{3-10} heterocyclyl, and C_{3-10} heterocyclyl substituted with C_{1-4} alkyl;
- C_{2-8} alkenyloxy;
- C_{3-8} cycloalkyl-C_{1-3} alkoxy, C_{5-10} aryl-C_{1-3} alkoxy, or C_{5-10} aryloxy, said C_{3-8} cycloalkyl-C_{1-3} alkoxy, C_{5-10} aryl-C_{1-3} alkoxy or C_{5-10} aryloxy optionally being substituted with 1, 2 or 3 groups selected from C_{1-4} alkyl, halogen, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, mercapto, hydroxy, cyano, nitro, a group of formula

$-N(R^c)_2$ in which the two R^c groups may be the same or different but not both simultaneously hydrogen;

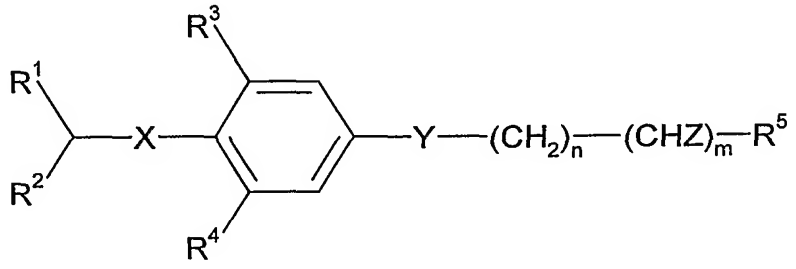
R^b is selected from hydrogen, halogen, hydroxyl, mercapto, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy and $(CH_2)_pOH$, where p is an integer from 1 to 4; and

R^c is selected from hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl and C_{2-4} alkynyl;

$R^{c'}$ is selected from R^c, C_{5-10} aryl or C_{5-10} aryl substituted with amino, hydroxyl, halogen or C_{1-4} alkyl; and

m is 1; or
simultaneously m is 0 or 1 and R^3 is C_{3-7} heterocyclyl; or
simultaneously Y is bond, m is 0, n is 0 and R^5 is $-CO_2R^c$.

10. A compound of formula (Ic) or a pharmaceutically acceptable ester, amide, solvate or salt thereof, including a salt of such an ester or amide, and a solvate of such an ester, amide or salt,



(Ic)

wherein:
R^1 is selected from C_{5-10} aryl, $C(O)$-C_{5-10} aryl, $C(O)$-C_{3-8} heterocyclyl or C_{5-10} heterocyclyl-C_{1-2} alkyl,

- said C(O)-C_{5-10} aryl, C(O)-C_{3-8} heterocyclyl or C_{5-10} heterocyclyl-C_{1-2} alkyl optionally being substituted with, where applicable, 1 to 3 groups $R^{a'}$ which may be the same or different;

- said C_{5-10} aryl being substituted with a group selected from:

  - C_{5-10} aryl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, mercapto, fluoromethyl, difluoromethyl, and C_{3-10} heterocyclyl-C_{2-4} alkenyl;
  - C_{2-4} alkenyl, substituted with 1, 2 or 3 groups selected from C_{5-10} aryl, $C(O)R^c$, C_{3-10} heterocyclyl, and C_{3-10} heterocyclyl substituted with C_{1-4} alkyl;
  - C_{2-8} alkenyloxy;
  - C_{3-8} cycloalkyl-C_{1-3} alkoxy, C_{5-10} aryl-C_{1-3} alkoxy, or C_{5-10} aryloxy, said C_{3-8} cycloalkyl-C_{1-3} alkoxy, C_{5-10} aryl-C_{1-3} alkoxy or C_{5-10} aryloxy optionally being substituted with 1, 2 or 3 groups selected from C_{1-4} alkyl, halogen, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, mercapto, hydroxy, cyano, nitro, a group of formula $-N(R^c)_2$ in which the two R^c groups may be the same or different but not both simultaneously hydrogen;

- said aryl optionally also substituted with, where applicable, 1 to 2 groups $R^{a'}$ which may be the same or different,

R^2 is selected from hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl and C_{1-4} alkoxy;

X is selected from CH_2, oxygen, sulfur, sulfoxide, sulfone, selenium, tellurium, disulfide, and a group of formula -$N(R^c)$-;

R^3 and R^4 are independently selected from hydrogen, halogen, C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{3-7} heterocyclyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio, trifluoromethylthio, and $COOR^c$;

Y is selected from bond, carbonyl, oxygen, sulphur, -$CH(R^b)$-, -NHCO-, -$NHSO_2$-, -SO_2NH-, -$N(R^c)$- and -CR^6=CR^7-;

n is selected from 0, 1, 2 and 3;

Z is selected from halogen, amino, hydroxy, mercapto, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy and $(CH_2)_pOH$, where p is an integer from 1 to 4;

m is selected from 0 and 1;

R^5 is selected from $-CO_2R^c$, $-PO(OR^c)_2$, $-PO(OR^c)NH_2$, $-SO_2OR^c$, $-COCO_2R^c$, $CONR^cOR^c$, $-SO_2NHR^c$, $-NHSO_2R^{c'}$, $-CONHSO_2R^c$, and $-SO_2NHCOR^c$;

R^6 and R^7 are independently selected from hydrogen, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{5-10}aryl, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, and $(CH_2)_pOH$, where p is an integer from 1 to 4;

R^a is selected from halogen, C_{1-4} alkoxy, C_{5-10} aryl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio, trifluoromethylthio, mercapto, cyano, and nitro;

$R^{a'}$ is selected from R^a, fluoromethyl, difluoromethyl, trifluoromethyl, C_{1-4} alkyl, and C_{3-10} heterocyclyl-C_{2-4} alkenyl;

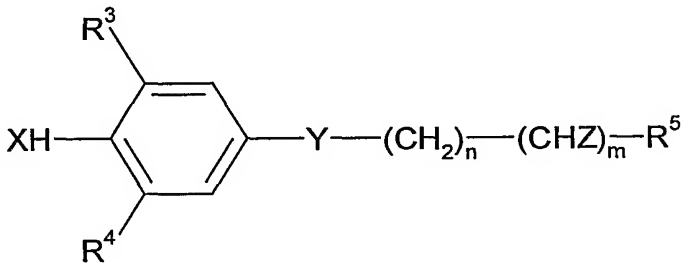
R^b is selected from hydrogen, halogen, hydroxyl, mercapto, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy and $(CH_2)_pOH$, where p is an integer from 1 to 4; and

R^c is selected from hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl and C_{2-4} alkynyl; and

$R^{c'}$ is selected from R^c, C_{5-10} aryl or C_{5-10} aryl substituted with amino, hydroxyl, halogen or C_{1-4} alkyl.

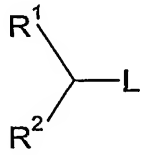
11. A compound as claimed in claim 9 or 10 for use as a medicament.

12. A method for preparing a compound of formula (Ib) as described in claim 9 or a compound of formula (Ic) as described in claim 10 comprising a step of adding a compound of formula (II)



(II)

wherein X, R^3, R^4, Y, n, Z, m and R^5 are as defined in claim 9 or 10, with a compound of formula (III)



(III)

wherein R^1 and R^2 are as defined in, as appropriate, claim 9 or 10 and L is a suitable leaving group, optionally in the presence of a suitable base.